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REVIEW ARTICLE

Uveitis Therapy: The Corticosteroid Options

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Abstract
Uveitis is characterized by intraocular inflammation involving the uveal tract; its etiologies generally fall into two broad categories: autoimmune/inflammatory or infectious. Corticosteroids are a powerful and important class of medications ubiquitous in the treatment of uveitis. They may be given systemically or locally, in the form of topical drops, periocular injection, intravitreal suspension, or intravitreal implant. This review describes each of the currently available corticosteroid treatment options for uveitis, including favorable and unfavorable characteristics of each as well as applicable clinical trials. The main advantage of corticosteroids as a whole is their ability to quickly and effectively control inflammation early on in the course of uveitis. However, they can have serious side effects, whether localized to the eye (such as cataract and elevated intraocular pressure) or systemic (such as osteonecrosis and adrenal insufficiency) and in the majority of cases of uveitis are not an appropriate option for long-term therapy.

Key Points

Corticosteroids are an important mainstay in the treatment of uveitis.

Corticosteroids can be given systemically or locally, in the form of topical drops, periocular injection, intravitreal suspension, or intravitreal implant; each option has its advantages and disadvantages.

In most cases of uveitis, corticosteroids are not appropriate long-term therapy due to their potentially damaging side effects.

1 Introduction

Uveitis is defined as inflammation of any of the three structures that make up the uvea: the iris, the ciliary body, and the choroid [1, 2]. Most etiologies of uveitis can be classified broadly as either infectious or autoimmune/inflammatory. Clinical features of uveitis include keratic precipitates, anterior chamber cell and flare, anterior and posterior synechiae, iris nodules, snowballs, snowbanks, vitreous haze and cells, choroidal lesions, and choroidal thickening. Uncontrolled uveitis can be complicated by cystoid macular edema, retinal vasculitis, optic nerve head edema, and subretinal fluid. A mainstay of treatment for uveitis and its sequelae is the use of corticosteroids.

The glucocorticoids are steroid molecules that are used to prevent or suppress inflammation. Among the cell types they affect are lymphocytes, macrophages, polymorphonuclear (PMN) leukocytes, vascular endothelial cells, and fibroblasts. The glucocorticoid molecules penetrate cell membranes and bind to soluble receptors in the cytosol. The resulting receptor/glucocorticoid complexes then translocate to nuclear binding sites for gene transcription and induce or suppress transcription of certain mRNAs. This process leads to the downregulation of expression of pro-inflammatory molecules (such as prostaglandins, leukotrienes, and thromboxanes) by blocking the enzyme responsible for conversion of phospholipids into arachidonic acid, which is converted into these molecules. At the same time, the expression of various cytokines is also downregulated [3, 4].

This review covers the current corticosteroid options for treatment of uveitis, including their advantages and disadvantages and relevant associated clinical trials.

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2 Topical Drop Therapy

The most common options for topical steroid therapy are prednisolone acetate suspension 1%, dexamethasone suspension 0.1%, difluprednate emulsion 0.05%, loteprednol etabonate suspension 0.5%, and fluorometholone (FML) suspension 0.1% (Table 1). Topical therapy is used primarily for anterior uveitis and is not generally efficacious for intermediate, posterior, or panuveitis.

The topical glucocorticoids vary in their potency and penetration; these properties are related to the structure of each molecule. Fluorination increases specificity for the glucocorticoid receptor [5]; this likely contributes to the effectiveness of the twice-fluorinated difluprednate. Acetates, such as prednisolone and difluprednate, penetrate the cornea most effectively. Loteprednol has an ester where most other topical steroids have a ketone—this leads to rapid inactivation and lower impact on intraocular pressure (IOP) elevation. Difluprednate has two esters, which help enhance its ability to penetrate tissue.

One study from 1975 compared the in vitro anti-inflammatory potency of six different topical steroids (including dexamethasone 0.1%, FML 0.1%, and prednisolone acetate 1%) based on the inhibition of lymphocyte transformation in an in vitro assay. Dexamethasone was the most potent, followed by FML and then prednisolone acetate [6]. However, in vivo, the relative potencies of the topical corticosteroids have proved difficult to determine. Prednisolone acetate penetrates better to the aqueous humor than either dexamethasone or FML [7]. While some drugs seem less likely to elevate IOP (please see Section 7), the overall trend based on the literature is that FML and loteprednol are not as effective as prednisolone acetate in controlling uveitis that is moderate or severe. Difluprednate is being used more frequently as its superior potency compared with prednisolone acetate becomes more well recognized [8]; it may penetrate to the vitreous more effectively than prednisolone acetate but also has a higher propensity for elevating IOP [9] and overall a high propensity for causing cataract [10].

The disadvantages of topical drop therapy in general compared with other means of steroid administration include need for frequent application, toxicity to the ocular surface from preservatives, and inability to penetrate to the posterior structures of the eye.

3 Periocular Therapy

Corticosteroids can be injected periocularly: either trans-septally or into the sub-Tenon's space [11]. The typical formulation injected in the periocular space is preserved triamcinolone acetonide 40 mg/mL. This method of delivery is advantageous in that it avoids systemic side effects and concentrates the steroid medication where it will be most effective; when treating macular edema, the aim is to inject the medication to be as close to the macula as possible. Usually the medication is injected with a 27-gauge needle as the particles are large enough that they may clog a 30-gauge needle. There are various injection techniques. For trans-septal injections, inferior injection into the orbital space through the eyelid is most common. For sub-Tenon's injections, the most common locations are superotemporally and inferiorly. Triamcinolone can be injected sub-Tenon's in different ways: posteriorly such that it is no longer visible on examination, or posteriorly at a site that is still visible, such that the depot can be removed relatively easily in case of steroid-induced ocular hypertension [11]. The adverse effects specific to the periocular mode of delivery are related to the site of injection. For superotemporal sub-Tenon's injections, ptosis from effects on the levator palpebrae can occur. For inferior trans-septal injections, fat prolapse through the septum from repeated injections can cause cosmetically bothersome lower lid thickening. Inadvertent penetration of the globe with risk

Table 1 Characteristics of different topical steroid drops

Topical steroid	Chemical properties	Other characteristics
Prednisolone acetate 1%	Acetate: penetrates cornea well	Most commonly used for uveitis in USA
Dexamethasone 0.1%	Fluorination: increased specificity for glucocorticoid receptor	Not commonly used by itself in USA
Difluprednate 0.05%	Double fluorination: increased specificity for glucocorticoid receptor Acetate: penetrates cornea well Double ester: increases tissue penetration	Superior potency compared with prednisolone May penetrate to vitreous Higher propensity for elevating IOP and causing cataract
Loteprednol etabonate 0.5%	Ester: rapid inactivation and lower impact on IOP elevation	Lower propensity for elevating IOP compared with prednisolone
Fluorometholone (FML) 0.1%	Fluorination: increased specificity for glucocorticoid receptor	Lower propensity for elevating IOP compared with prednisolone

of retinal tear and detachment is a rare but serious complication with periocular injections.

4 Intravitreal Therapy

Intravitreal corticosteroid therapy can be useful for certain types of noninfectious uveitis that involve the posterior segment of the eye in patients who have failed or cannot tolerate the side effects of immunomodulating therapy or to treat vision-threatening inflammation or macular edema in the short term while bridging patients to longer term immunomodulatory therapy. Preservative-free triamcinolone acetonide 40 mg/mL (Triesence, Alcon Laboratories, Inc.) can be injected intravitreally. In recent years, the use of sustained-release steroid implants has become more prevalent. Among the available options are a non-biodegradable 0.59-mg fluocinolone implant (Retisert, Bausch and Lomb, Inc.) that must be sutured to the sclera, a non-biodegradable 0.19-mg fluocinolone injectable intravitreal implant (Iluvien 0.19 mg, Alimera Sciences, Inc.), a biodegradable 0.7-mg dexamethasone injectable intravitreal implant (Ozurdex, Allergan, Inc.), and most recently a non-biodegradable 0.18-mg fluocinolone injectable intravitreal implant (Yutiq, Eyepoint Pharmaceuticals, Inc.).

4.1 Preservative-Free Triamcinolone Acetonide

Preservative-free triamcinolone acetonide 40 mg/mL is injected intravitreally, usually in the amount of 4 mg in 0.1 mL, using a 27-gauge needle. It is FDA approved for use during vitrectomy to stain and enable visualization of the vitreous, in ocular inflammation that does not respond to topical corticosteroids, and in sympathetic ophthalmia. Its effect is rapid and can last up to 3 months, but overall it has the shortest duration of action of all the injectable corticosteroid formulations. It has been studied regarding its utility in treating the cystoid macular edema (CME) that can complicate uveitis [12] as well as the uveitis itself [13–23].

One particular study involving administration of preservative-free triamcinolone in 54 patients with uveitis-related CME who failed periocular steroids, oral steroids, and second-line immunomodulating therapy (IMT) found that the medication helped resolve CME, improve visual acuity, and in certain cases reduce or eliminate the need for further systemic treatment [12]. One randomized controlled clinical trial that compared preservative-free triamcinolone injection to sham injection with systemic therapy for uveitis-related CME in 50 patients showed that triamcinolone accelerated the resolution of CME as well as leakage on fluorescein angiography compared with solely systemic therapy [24]. The disadvantage specific to intravitreal triamcinolone is a duration of effect of < 6 months [25], potentially requiring repeat injections depending on the severity of the case, each time with the known risks of intravitreal injections.

4.2 Fluocinolone Acetonide 0.59 mg Implant

The non-biodegradable 0.59-mg fluocinolone implant (Retisert, Bausch and Lomb, Inc.) is made of polyvinyl acetate and silicone and contains a pellet of steroid medication. It is placed surgically, via pars plana sclerotomy, and sutured to the sclera. The implant releases steroid at a rate of about 0.3–0.4 μg/day and can last up to about 3 years [26]. This implant is approved for treatment of noninfectious intermediate, posterior, and panuveitis. Its cost can range from around 13,000 to 20,000 US dollars. Some studies have shown that it is cost effective compared with systemic therapy in cases of unilateral intermediate, posterior, or panuveitis [27].

There is a large body of literature concerning the efficacy of the 0.59-mg fluocinolone implant [28–34]. One multicenter clinical trial compared the implant with systemic treatment with steroids and additional IMT as needed amongst 140 patients with noninfectious posterior uveitis; inflammation took longer to recur in patients who received the implant, and while 63.5% of patients who received only systemic therapy experienced a recurrence, only 18.2% of patients who received the implant experienced a recurrence [29]. The most well-known randomized clinical trial comparing the 0.59-mg fluocinolone implant to systemic IMT is the Multicenter Uveitis Steroid Treatment (MUST) trial. It involved 479 uveitic eyes of 255 patients; at 24 months, 88% of patients in the fluocinolone implant treatment arm achieved control of their uveitis compared with 71% in the systemic treatment (systemic corticosteroids + immunomodulating therapy when indicated) arm; this difference was statistically significant. However, there was no statistically significant difference regarding improvement in visual acuity between the two arms in the original MUST trial [30]. There was comparable incidence of systemic adverse effects between the two arms; the patients on systemic therapy had higher risk of systemic infection requiring antibiotics. Further investigation involving both treatment groups after a longer follow-up period has shown that visual acuity outcome at 7 years is significantly better in the group that received systemic therapy as opposed to the group that received the implant [33].

While the 0.59-mg fluocinolone implant can advantageously last for 2–3 years, in some cases the chronic inflammation can outlast this time period and additional implants may be needed. In the MUST trial, after 54 weeks of follow up, about 8% of eyes had required two implants, and 2% of eyes had required three implants [34]. The side effects specific to the procedure for the insertion of this implant include hypotony and dissociation of the implant pellet requiring additional surgery. Postoperative hypotony can

occur if wound closure is not performed correctly; one trial observed hypotony in about 25% of the 239 patients that received the implant; two of these patients had wound leak and required removal of the implant. There have been multiple accounts of dissociation of the implant requiring removal by pars plana vitrectomy [35–37]. The incidence of dissociation of the implant is 4–5%, depending on the study [38, 39]. To address the issue of dissociation, a redesigned Retisert implant with a silicone suture strut was introduced in 2013.

4.3 Fluocinolone Acetonide 0.19 mg Implant

The non-biodegradable 0.19-mg fluocinolone implant (Iluvien, Alimera Sciences Inc.) consists of a drug-polyvinyl–polyamide rod measuring 3.5 mm long and 0.37 mm in diameter [40] that costs about 9000 US dollars. It is injected intravitreally through the pars plana with a 25-gauge needle and lasts for up to 3 years, releasing steroid at a rate of 0.2–0.5 µg/day [41]. Currently it is US FDA-approved to treat diabetic macular edema, but not uveitis. It was approved for treatment of non-infectious posterior uveitis in several European countries in 2019, based on two randomized controlled multicenter phase III trials [42]. Compared with the 0.59-mg fluocinolone implant, this implant is advantageous in that it can be injected in the office setting and does not need to be secured to the sclera. The polyvinyl–polyamide rod carrier is not biodegradable and thus will remain in the eye after the fluocinolone effect has ended. Migration of the rod into the anterior chamber, with subsequent anterior chamber inflammation, in eyes with a compromised posterior intraocular lens capsule is a side effect to keep in mind [43]. This implant should not be injected into aphakic eyes or pseudophakic eyes with a compromised posterior capsule because of this potential adverse effect.

4.4 Dexamethasone 0.7 mg Implant

The biodegradable 0.7-mg dexamethasone implant (Ozurdex, Allergan, Inc.) is also an injectable intravitreal implant that is administered through a 22-gauge applicator through the pars plana. It consists of a lactic acid–glycolic acid polymer matrix combined with dexamethasone and costs around 1500 US dollars. It is designed to release the drug over a period of up to 6 months, but in the majority of patients its effect wanes within 3–4 months [44]; peak concentrations are reached in about 2 months and are similar whether the eye has undergone vitrectomy or not [45]. This implant is FDA-approved for the treatment of noninfectious uveitis. One clinical trial investigating safety and efficacy of the 0.7-mg dexamethasone implant involved 229 patients randomized to either treatment with a 0.35-mg implant, a 0.7-mg implant, or sham. After 26 weeks, visual acuity was significantly better in the patients treated with dexamethasone compared with the sham group. The group that received the 0.7-mg implant had a significantly higher proportion of patients with resolution of vitreous haze compared with the other groups at both 8 and 26 weeks out from the time of treatment. The fact that about 25% of patients treated with the 0.7-mg implant achieved resolution of vitreous haze by 3 weeks suggests that the medication becomes effective relatively quickly [46]. Other trials have shown that the 0.7-mg dexamethasone implant is also efficacious for uveitic macular edema and for treatment of uveitis in combination with systemic therapy [44, 47–49]. As with the 0.19-mg fluocinolone implant, the 0.7-mg dexamethasone implant is easier to administer compared with the 0.59-mg fluocinolone implant, but of course carries the usual risks of any intravitreal injection. The need for repeated administration in cases of chronic inflammation is one of its disadvantages. The side effect of migration into the anterior chamber as described for the 0.19-mg fluocinolone implant above also applies to the 0.7 mg dexamethasone implant, although since the device biodegrades completely, this risk is not lifelong [50].

4.5 Fluocinolone Acetonide 0.18 mg Implant

The newest formulation of fluocinolone comes as an injectable 0.18-mg implant (Yutiq, Eyepoint Pharmaceuticals, Inc.) approved for the treatment of chronic noninfectious posterior uveitis in the United States. It consists of a polyamide cylinder with the steroid at the core and has a length of 3.5 mm and a diameter of 0.37 mm (like the 0.19-mg fluocinolone implant); it costs around 8000–9000 US dollars. Designed to prevent rather than treat uveitis flare-ups, it is meant to release steroid consistently and slowly at a rate of 0.1–0.2 µg/day and can last up to 3 years [51]. A phase III study involving 129 patients with noninfectious posterior uveitis showed that patients in the treatment arm had statistically significantly lower rates of uveitis recurrence compared with patients in the sham arm: at 6 months, 27.6% of treated patients experienced a recurrence compared with 90.5% of the control patients, and at 12 months, 37.9% of treated patients experienced a recurrence compared with 97.6% of the control patients [52]. Like the 0.7-mg dexamethasone implant, the 0.18-mg fluocinolone implant can be administered in the office setting with a special applicator, but it may prove advantageous over the 0.7-mg dexamethasone implant in that it delivers a low dose of steroid over several years as opposed to several months, theoretically decreasing the burden of repeat injections as well as the potential for progressive damage from flares between injections when the medication has worn off. However, the 0.18-mg fluocinolone formulation is less potent than the 0.7-mg dexamethasone implant [53] and therefore may not suppress inflammation as well in cases of more severe inflammation. It also has about a third of the fluocinolone dose of the 0.59-mg fluocinolone

implant and is thus similarly less potent when compared with that device. As with the 0.19-mg fluocinolone implant, the carrier is not biodegradable and has the potential for migration into the anterior chamber with resultant anterior chamber decompensation.

5 Suprachoroidal Therapy

The injection of therapeutic medications in the suprachoroidal space in order to achieve more focused delivery and avoid some of the adverse effects of intravitreal injections, such as retinal detachment, endophthalmitis, and cataract, has been explored since before 2006 [54–56]. Preservative-free triamcinolone acetate 4 mg/0.1 mL administered in the suprachoroidal space with a special microinjector engineered by Clearside Biomedical, Inc. (CLS-TA) has been tested in patients with noninfectious intermediate, posterior, and panuveitis. Initial phase I and II trials (one involving 9 patients and one involving 22 patients) showed promising efficacy, measured by improvement in visual acuity and reduction of macular edema, as well as safety [57, 58]. The phase III trial, PEACHTREE, involved 160 patients with uveitic macular edema; 96 patients were randomized to the treatment arm and received two doses of CLS-TA 12 weeks apart. The primary endpoint was the proportion of patients gaining 15 or more letters of best corrected visual acuity (BCVA) at week 24. At this time point, the treatment group showed significant improvement in BCVA as well as central subfield thickness of the retina compared with the control group [59]. This agent has not become commercially available at the time of publication. The specific side effects to this form of delivery are the potential for inadvertent injection into the vitreous (reported in one patient in a study involving patients with diabetic macular edema) [60] and theoretical risk of suprachoroidal hemorrhage, of which there are no published reports as of yet.

6 Systemic Therapy

The most common systemic corticosteroids administered are oral prednisone and intravenous methylprednisolone. These drugs are fast acting and are usually used to quickly rein in severe inflammation. In a minority of very severe cases of uveitis, such as certain cases of Vogt-Koyanagi-Harada disease, methylprednisolone is given intravenously in the form of 1 g daily for 3 days in a row as a protocol to quell fulminant inflammation [61]. After methylprednisolone, or as a starting medication in cases not requiring methylprednisolone, prednisone is usually administered at a starting dose of 1 mg/kg daily (avoiding doses of 60 mg daily or more if possible because of increased risk of osteonecrosis with higher doses) and tapered slowly over many weeks [62]. The side effects of long-term systemic steroid use are well known and include but are not limited to skin striae, easy bruising and bleeding, hypokalemia, hyperglycemia and diabetes, Cushingoid appearance (moon facies, buffalo hump, central obesity), weight gain, osteoporosis and osteonecrosis, adrenal insufficiency, cardiovascular disease, and immunosuppression [63]. Based on the present literature, a maintenance dose of 7.5 mg or less per day of prednisone minimizes the most serious long-term adverse effects of systemic glucocorticoid therapy [62]. Overall, the goal in the treatment of uveitis is to spare patients from the deleterious, often life-threatening long-term side effects of systemic steroids by using either local steroid therapy, or, even better, steroid-sparing immunomodulating therapy for long-term use when a daily maintenance dose of prednisone 7.5 mg or less cannot be achieved within 3–6 months.

7 Main Adverse Effects of Localized Steroid Therapy—Cataract and Glaucoma

The two most well-known ocular adverse effects of steroid therapy are cataract [64] and IOP elevation [65].

The type of cataract induced by steroid use is commonly a posterior subcapsular cataract [64]. When visually significant, cataract surgery can be performed, but can become complicated depending on the age of the patient (cataract surgery is not ideal in children as their eyes are growing and the absence of a natural lens that can adapt to the growing eye can lead to amblyopia) and other sequelae of uveitis that can make the surgery more difficult (e.g., synechiae that need to be lysed or a pupillary membrane that needs to be removed). Of course, all the usual risks of cataract surgery apply as well.

High IOP can lead to glaucoma, a dreaded sequela of steroid treatment. About 30–40% of the general population will experience elevated IOP of 5 mmHg or more while on corticosteroids, and nearly all patients with primary open-angle glaucoma (POAG) are steroid responders. Risk factors for IOP elevation in response to steroid use include, along with history of POAG, a first-degree relative with POAG, young age (< 6 years), older age, connective tissue disease, myopia, and previous steroid response [66]. Responsiveness also depends, logically, on the duration, potency, frequency, and modality of steroid administered [65]. Generally, local steroid therapy is more likely to cause cataract and glaucoma compared with systemic therapy. Steroid-induced IOP elevation rarely occurs in < 5 days, but after this checkpoint it can develop at any time [66]. Once steroids are stopped, the IOP elevation usually resolves within a time course similar to or slightly longer than the length of time of onset of IOP elevation. It is usually reversible by discontinuing therapy if

the drug has been used for < 1 year, and is more likely to be permanent if therapy has continued for 18 months or longer.

Steroid-induced IOP elevation is thought to be due to increase resistance to aqueous outflow in the trabecular meshwork (TM) due to inhibited degradation and/or enhancement of deposition of extracellular matrix material in the TM. Other mechanisms may include inhibition of phagocytosis (which clears outflow channels of debris) by cells in the TM and cross-linking of actin fibers in the TM. It is unclear based on the present literature whether or not myocilin may have a role in steroid-induced ocular hypertension [67].

The same features that give each topical glucocorticoid its potency also affect each drug's tendency to raise IOP. Loteprednol is an example of a newer-generation drug designed with the intent to lower the degree of steroid-induced IOP elevation. Trends from various studies include the following: difluprednate, although superior in potency, also causes higher IOP elevation compared with other topical steroids; FML causes significantly less IOP elevation compared with prednisolone acetate and dexamethasone; prednisolone causes higher IOP elevation compared with loteprednol [68].

The risk for steroid-induced IOP rise is substantial for periocular and intravitreal steroid formulations. In one particular study investigating intravitreal triamcinolone, IOP elevation was the primary adverse effect, developing in 33–41% of patients. About a third of patients were treated successfully with medical therapy, and 1–2% of patients required glaucoma surgery within the first year of steroid treatment. About a third of patients required cataract surgery within the first year of treatment as well [24]. Regarding the 0.59-mg fluocinolone implant, the MUST trial showed that the incidence of cataract and glaucoma were significantly lower in the systemic immunomodulatory therapy arm compared with the implant treatment arm. Combining data from various 0.59-mg fluocinolone implant trials, 80–93% of phakic patients with the implant developed cataract, and 26–37% of eyes required glaucoma surgery for elevated IOP [29–32]. The incidence of cataract in one trial involving the 0.19-mg fluocinolone implant for diabetic macular edema in phakic patients was 81.7% in the treatment arm, compared with 50.7% of patients in the sham arm. IOP elevation occurred in 37.1% of patients treated with the 0.19-mg fluocinolone implant compared with 11.9% of patients in the sham arm. Of the patients with elevated IOP, 3.8% required laser trabeculoplasty and 12.9% required glaucoma surgery [68]. While the 0.7-mg dexamethasone implant can cause cataract as well, the incidence of cataract formation among patients who received the 0.7-mg dexamethasone implant for diabetic macular edema or vein occlusions is less than that of patients receiving the 0.59-mg fluocinolone implant [69, 70]. In one 0.7-mg dexamethasone implant clinical trial, elevated IOP occurred in about 10% of eyes treated with the implant, and resolved in most cases in 6 months or less with medical therapy [44]. However, the results for this 0.7-mg dexamethasone implant trial pertain to one injection only and do not completely reflect the risk of IOP rise in the real world where patients often require many injections. There is one retrospective review that investigated the effect on IOP of multiple 0.7-mg dexamethasone implant injections over time; out of 171 patients, 25 eyes received two injections, and 19 received three. The conclusion was that multiple injections did not increase the frequency of IOP spikes > 30 mmHg; however, the number of patients who received repeated injections was relatively small [71]. In the main clinical trial for the 0.18-mg fluocinolone implant, 26% of patients who received the implant required IOP-lowering medications for IOP elevation. After 12 months of treatment, 33% of the treatment patients required cataract surgery compared with 12% of control patients [52].

Administration of triamcinolone in the suprachoroidal space is promising in that it appears to avoid the adverse effects of cataract and glaucoma by keeping the steroid sequestered posterior to the choroid and retina, away from the vitreous and aqueous humor. The PEACHTREE trial noted that 11.5% of patients in the treatment group experienced elevated IOP compared with 15.6% in the control group, and there was no significant difference in the rate of cataract formation between the treatment and control groups (7.3% and 6.3%, respectively) [59].

8 Conclusion

The corticosteroids are a double-edged sword in the realm of uveitis. They are essential early on in the treatment of uveitis, when rapid control of inflammation is crucial. Steroids can be given systemically, or locally, whether in the form of topical drops, a periocular injection, an intravitreal suspension, or an intravitreal implant, of which there are several variations, each with their risks and benefits as detailed above (Table 2). However, they all can have significant adverse effects, ranging from the cataracts and glaucoma caused by local therapy to the life-threatening effects of high-dose, long-term systemic steroids such as adrenal insufficiency and diabetes. Use of corticosteroids, whether local or systemic, is not an appropriate option for long-term therapy of uveitis in most cases. Steroid-sparing immunomodulating therapy is often the best option in such chronic cases.

Table 2 Advantages and disadvantages of each method of delivery of steroid

Delivery method	Advantages	Disadvantages
Topical drops	Minimal systemic side effects Can be administered at home	Primarily useful for anterior uveitis Can cause IOP elevation, glaucoma Can cause cataract Can cause toxicity from preservatives
Periocular	Minimal systemic side effects Longer effect compared with drops Can reach posterior pathology	Can cause IOP elevation, glaucoma Can cause cataract May not be able to be removed May need to be repeated
Intravitreal	Minimal systemic side effects Longer effect compared with drops Can target posterior pathology	Can cause IOP elevation, glaucoma Can cause cataract Difficult to remove if necessary Depending on the type of drug and/or implant, may need repeated administration as it wears off Certain implants may dissociate and/or migrate within the eye
Suprachoroidal	Minimal systemic side effects In theory, targets posterior pathology without elevating IOP or causing cataract	Not currently commercially available
Systemic	Fast-acting Less likely to cause cataract and glaucoma compared with local therapy	Can cause serious systemic side effects, including osteonecrosis, diabetes, weight gain, adrenal insufficiency, cardiovascular disease, and immunosuppression

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Compliance with Ethical Standards

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Conflict of interest Dr. Sobrin is a consultant for Clearside Biomedical, Inc. Dr. Valdes has no conflicts of interest.

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